REMARKS

I. Status of the Claims

Claims 1, 4, 5, 8, and 10-12 are amended

Claim 6 is canceled

Claims 1-5, 7-12 are pending.

II. Claim Formats are Amended

Applicants thank the examiner for withdrawing rejection of claims 1-11. Claims 8 and 10 are amended to remove objections to format.

With regard to the present rejections, claims 1, 4, 5, 11-12 are amended. The examiner believes there were no limitations on "a set of standard solutions with predetermined characteristics" that may be used in a test kit of claim 11. Every one of the examples in the patent application describes solutions with predetermined characteristics that may be packaged into a kit as standard solutions. Those of skill in the art would know what was needed to test compounds of interest to them. Guidance is also clear from the specification. The meaning of "solutions with predetermined characteristics" is clear from the examples in the specification, e.g. at least at the following locations".

Page	Line	Comment
2	10-11	The present invention provides a method for determining whether a compound has predetermined characteristics that make it a candidate for drug development or a substrate for a particular enzyme.
3	7-10	

A kit would contain, for example, a specific enzyme (such as the specific isozyme cytochrome P450 3A4 or a mixture of cytochrome P450 isozymes contained in liver microsomes), a buffer (pH 7.4 40 mM ammonium acetate or a powder that would be reconstituted just by adding water), and the necessary cofactor NADPH. The user would reconstitute the buffer, and use the buffer to deliver the enzyme solution (or suspension) to the ultrafiltration chamber. The user would then inject a test sample (selected by the user) into the chamber along with the cofactor NADPH. The metabolic product(s) contained in the ultrafiltrate would then be analyzed from the second

solution probably using mass spectrometry to see if a compound of interest had predetermined characteristics.

On page 3 of the Office Action, the examiner admits that the specification is "enabling for the predetermined characteristics recited in claim 6," so incorporating elements of claim 6 into claims 1 and 11 should render claims 1 and 11 allowable.

Claim 6 defines these predetermined characteristics and limits them to substrates for an enzyme, showing desirable rates of enzymatic catalysis, showing desirable rates of cell permeability or transport, or showing enzymatic activation to reactive or toxic metabolites.

The term "supportive solution" (page 3, lines 1-3 of the specification) is used to convey that the liquid phase that flows through the ultrafiltration chamber must be compatible with the high molecular weight and low molecular weight substances present in the chamber. When the high molecular weight substance is an enzyme such as a cytochrome P450 and the low molecular weight substance is a drug substance, then the supportive solution must be appropriate to maintain the enzyme in its active state and facilitate the interaction of the drug with the enzyme. For example, one skilled in the art would know that a buffer would be required to maintain the pH at the physiological level of pH 7.4 and the temperature should be from room temperature to physiological temperature at 37° C. The term "suitable" is defined in the specification at least *e.g.* on page 6 lines 7-8, and would be known to those of skill in the art depending on the purpose of the test.

The examiner stated that in claim 3, that it was not clear how the "compound" (singular) recited in the preamble can be a "combinatorial library," "a drug mixture," "a mixture of xenobiotic compounds," or "a mixture of endogenous compounds" (all pluralities) and requested clarification. The "compound" in question is simply a low molecular weight substance or substances that interact with the high molecular weight material contained within the ultrafiltration chamber. The "compound" may be a single substance or a group of substances and may be selected from among a group that includes a plurality of compounds.

III. Venton Neither Anticipates Claims 1-5, 7-11 Nor Makes Claim 12 Obvious

Venton *et al.* does not teach all the elements of independent claims 1 or 11, and therefore does not satisfy the legal criteria for anticipation. As the examiner admits,

> The use of a continuous flow cell and separation by ultrafiltration of the products of contacting biological samples with solutions of compounds to determine any predetermined characteristic was not known in the art. Using such a method to identify compounds with predetermined characteristics such as curing cancer or Alzheimer's Disease or regenerating a damaged spinal cord were highly unpredictable in the art. The inventors have provided working examples with respect to cytochrome P450 and bioavailability assays and assays for glutathione adduct formation. Direction has been provided with respect to biological assays such as toxicity, enzymatic activation/inactivation, and cell permeability and transport.

Action, page 4

Venton *et al.* does not teach all the claimed elements. Differences between the Venton patent and the pending application include:

In the present application, the amount of compounds in the ultrafiltrate are measured. (page 14, lines 25-34 and page 15, lines 1-3 of the application). The Venton application is not quantitative; Venton is only qualitative. In the present application, it is necessary to measure the amounts of compounds in the ultrafiltrate in order to determine the rate at which compounds are metabolized or degraded. This is an example of measuring metabolic stability. For example in claim 6, "rates of enzymatic catalysis" requires measurement.

In another aspect of the application, the rate at which compounds cross a cell membrane must be measured. This is another quantitative analysis and is part of the high throughput determination of bioavailability. For example, to fulfill claim 6, "rates of cell permeability or transport" must be measured. The Venton patent does not involve any quantitative determination. Furthermore, the

Venton patent did not involve cell permeability studies. Instead, the Venton patent concerned the affinity interaction of low molecular weight compounds with a "macromolecular receptor."

Another difference between the present application and the Venton patent is the use of living cells. The Venton application concerns the use of a "predetermined target macromolecule in solution" (Venton Claim 1). The present application can involve living cells or microsomes which are not in solution. Living cells cannot be solubilized. Claim 1 of the present invention allows for "suspension." Although Venton teaches the use of whole cells (column 20 lines 52-55), the purpose there is to screen cells for the discovery of new receptors. The present application uses whole cells as a living entity for the purpose of determining cellular permeability to a compound or mixture of compounds under investigation. In another application, the present invention uses living cells for the purpose of investigating rates of formation of metabolites or to facilitate the formation of metabolites of compounds under investigation.

The present application includes the use of enzymatic transformation and the identification of metabolites of the test substances. The claims of the Venton application do not mention enzymes or metabolism. This is another important difference.

The quantitative aspects of the present invention and the use of living cells or active enzymes to produce metabolites are all completely unique and are not anticipated by Venton. With respect to quantitative analysis or measuring rates, here are some other examples to help differentiate the pending application from the Venton patent:

Example 3. High Throughput Metabolic Screening

last sentence. "The high throughput analyses of the present invention may also be used quantitatively to assess the extent of metabolism by measuring the disappearance of drug during incubation

to assess the extent of metabolism by measuring the disappearance of drug during incubation compared to control incubations that use inactive microsomes or no NADPH cofactor."

Example 8. Rapid Intestinal Transport Assay

"The graphs in FIG. 11 show straight lines, and the ratio of the slopes of these lines represents the relative elution rates for aspirin and propranolol, aspirin/propranolol = 1.6:1."

Detailed Description of the Invention

(5 paragraphs before the Examples section) "Metabolites may be detected, identified and quantified on-line using a mass spectrometer..."

(3 paragraphs before the Examples section) "In this manner, quantitative bioavailability or absorption data may be determined."

(2 paragraphs before the Examples section) "3) quantitation of each product or metabolite and the amount of unchanged substrate. Measurement of the rate of disappearance of the substrate provides a measure of how extensively one compound is metabolized compared to another."

(last paragraph of Detailed Description section) "2) how rapidly and extensively a compound is metabolized relative to other substances,"

Although the examiner admits that Venton *et al.* does not teach the use of multiple chambers in parallel of claim 12, he suggests that this arrangement would be obvious. The parallel arrangement of chambers with a single mass spectrometer for the type of high throughput screening being carried out here is unique to this invention.

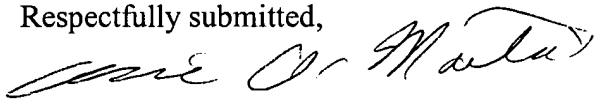
The time at which each chamber in the array is sampled is not obvious. It has neither been thought nor suggested in the publications cited. The sampling time should coincide with the anticipated maximum amount of metabolites eluting from the chamber.

V. Summary and Conclusion

For the reasons stated above, applicant requests allowance of claims 1-5, 7-12.

No other fees are believed due at this time, however, please charge any deficiencies or credit any overpayments to deposit account number 10-0435 with reference to our attorney docket number (21726/90386).

Respectfully submitted,



Alice O. Martin
Registration No. 35,601

Barnes & Thornburg
2600 Chase Plaza
10 South LaSalle Street
Chicago, Illinois 60606
(312) 214-8316
March 5, 2002
::ODMA\MHODMA\CHDS01;125235;1

MARKED UP VERSION COPY OF PENDING CLAIMS
SERIAL NO. 09/471,523

WE CLAIM

1. (Twice Amended) A method for determining whether a compound from a sample has predetermined characteristics that would make it suitable for a specific purpose, said purpose comprising drug development and screening for metabolic parameters, said method comprising:

a. obtaining a biological material in a first solution or suspension;

b. [maintaining a continuous] inducing a flow of a supportive solution through the first solution or suspension;

c. adding the sample to the continuous flow of the supportive solution;

d. reacting the biological material in the first solution or suspension with the compound in the sample to provide metabolites, or to assess permeability and bioavailability;

e. washing the results of the reacting between the biological material in the first solution and the compound in the sample through an ultrafiltration membrane to form a second solution; and

f. analyzing the second solution to determine whether the compound in the sample has the predetermined characteristics, wherein the predetermined characteristics are selected from the group consisting of functioning as a substrate for an enzyme, showing desirable rates of enzymatic catalysis, showing desirable rates of cell permeability or transport, and showing enzymatic activation to reactive or toxic metabolites.

4. (Amended) The method of claim 1, wherein the supportive solution is selected from a group consisting of a buffer, a nutrient medium, or a combination thereof, said supportive solution [capable of] maintaining the biological material in a state wherein the biological material [can interact] interacts with a compound in the sample.

5. (Amended) The method of claim 1, wherein the continuous flow facilitates the reacting of the biological material with the sample in the first solution or suspension and

facilitates the removal of compounds [and their metabolites] from the sample by washing them through the ultrafiltration chamber into the second solution.

[6. The method of claim 1, wherein the predetermined characteristics consist of functioning as a substrate for an enzyme, showing desirable rates of enzymatic catalysis, showing desirable rates of cell permeability or transport, showing enzymatic activation to reactive or toxic metabolites.]

8. (Twice Amended) The method of claim 1, wherein the suitable conditions for reacting of the biological material in the first solution with the compound in the sample comprises mixing the sample with the biological material to achieve a homogeneous distribution of sample, temperature control to maintain function of the biological material, adequate concentration of sample and sufficient amount of biological material to facilitate analysis, sufficient time for interaction[,] and control of atmospheric gases (oxygen and carbon dioxide) to maintain function of the biological material.

10. (Amended) The method of claim 1, [whereas] wherein the analyzing of the second solution is by mass spectrometry.

11. (Amended) A kit for analyzing [compounds] a compound in a sample, to determine whether the compound has predetermined characteristics that would make it suitable for a specific purpose, said purpose comprising drug development and screening for metabolic parameters, said kit comprising in separate containers, an ultrafiltration membrane, a first solution containing a biological material, a buffer, a test solution, and a set of standard solutions with predetermined characteristics wherein the predetermined characteristics are selected from the group consisting of functioning as a substrate for an enzyme, showing desirable rates of enzymatic catalysis, showing desirable rates of cell permeability or transport, and showing enzymatic activation to reactive or toxic metabolites.

12. (Amended) The method of claim 1, wherein multiple chambers with ultrafiltration membranes are arranged in parallel with a single mass spectrometer for steps e and f.

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WE CLAIM

1. A method for determining whether a compound from a sample has predetermined characteristics that would make it suitable for a specific purpose, said purpose comprising drug development and screening for metabolic parameters, said method comprising:

a. obtaining a biological material in a first solution or suspension;

b. inducing a flow of a supportive solution through the first solution or suspension;

c. adding the sample to the continuous flow of the supportive solution;

d. reacting the biological material in the first solution or suspension with the compound in the sample to provide metabolites, or to assess permeability and bioavailability;

e. washing the results of the reacting between the biological material in the first solution and the compound in the sample through an ultrafiltration membrane to form a second solution; and

f. analyzing the second solution to determine whether the compound in the sample has the predetermined characteristics, wherein the predetermined characteristics are selected for the group consisting of functioning as a substrate for an enzyme, showing desirable rates of enzymatic catalysis, showing desirable rates of cell permeability or transport, and showing enzymatic activation to reactive or toxic metabolites.

2. The method of claim 1, wherein the biological material is selected from a group consisting of a protein, a peptide, an oligonucleotide, an oligosaccharide, a microsome, a cell, a tissue, an enzyme, a receptor, DNA and RNA.

3. The method of claim 1, wherein the compound is selected from the group consisting of a natural product, a combinatorial library, a drug, a drug mixture, a xenobiotic compound, a mixture of xenobiotic compounds, an endogenous compound, and a mixture of endogenous compounds.

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4. The method of claim 1, wherein the supportive solution is selected from a group consisting of a buffer, a nutrient medium, or a combination thereof, said supportive solution maintaining the biological material in a state wherein the biological material interacts with a compound in the sample.

5. The method of claim 1, wherein the continuous flow facilitates the reacting of the biological material with the sample in the first solution or suspension and facilitates the removal of compounds from the sample by washing them through the ultrafiltration chamber into the second solution.

7. The method of claim 1, wherein the sample is added to the continuous flow by means of injection.

8. The method of claim 1, wherein the suitable conditions for reacting of the biological material in the first solution with the compound in the sample comprises mixing the sample with the biological material to achieve a homogeneous distribution of sample, temperature control to maintain function of the biological material, adequate concentration of sample and sufficient amount of biological material to facilitate analysis, sufficient time for interaction, and control of atmospheric gases (oxygen and carbon dioxide) to maintain function of the biological material.

9. The method of claim 1, wherein the ultrafiltration membrane has pore sizes that allow the sample molecules to pass through but not the biological material.

10. The method of claim 1, wherein the analyzing of the second solution is by mass spectrometry.

11. A kit for analyzing a compound in a sample, to determine whether the compound has predetermined characteristics that would make it suitable for a specific purpose, said purpose comprising drug development and screening for metabolic parameters, said kit comprising in separate containers, an ultrafiltration membrane, a first solution containing a biological material, a buffer, a test solution, and a set of standard solutions with predetermined characteristics wherein the predetermined characteristics consist of functioning as a substrate for an enzyme,

showing desirable rates of enzymatic catalysis, and showing desirable rates of cell permeability or transport, showing enzymatic activation to reactive or toxic metabolites.

12. The method of claim 1, wherein multiple chambers with ultrafiltration membranes are arranged in parallel with a single mass spectrometer for steps e and f.